08/808261

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REQUEST FOR FILING A PATENT APPLICATION UNDER 37 C.F.R. § 1.60

Docket Number	Anticipated Classification of this Application		Prior Application
1611.0510002	Class:	Subclass:	Examiner: J. Peabody Art Unit: 1201

Address to:
Assistant Commissioner for Patents
Box Patent Application
Washington, D.C. 20231

This is a request for filing a ☒ continuation ☐ divisional application under 37 C.F.R. § 1.60 of pending prior application no. 08/154,403, filed on November 19, 1993 entitled **Microencapsulated 3-Piperidynyl-Substituted 1,2-Benzisoxazoles and 1,2-Benzisothiazoles**.

1. ☒ Enclosed is a copy of the latest inventor-signed prior application, including a copy of the oath or declaration showing the original signature or an indication it was signed. I hereby verify that the papers are a true copy of the latest signed prior application number 08/154,403, and further that all statements made herein of my own knowledge are true; and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like are made punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issuing thereon.

Claims	(1) For	(2) Number Filed	(3) Number Extra	(4) Rate	(5) Calculations
	Total Claims*	3 - 20 =	0	x $ 22 =	$0.00
	Independent Claims*	2 - 3 =	0	x $ 80 =	$0.00
	Multiple Dependent Claim(s)* (if applicable)			+ $ 260	$0.00
				Basic Fee	$ 770.00
				Total of above calculations =	$ 770.00
	Reduction by 1/2 for filing as small entity (Note 37 C.F.R. §§ 1.9, 1.27 and 1.28).				
				GRAND TOTAL =	$ 770.00

*The filing fee is calculated on the basis of the claims existing in the prior application as amended at 5. and 11.

2. A verified statement to establish small entity status under 37 C.F.R. §§ 1.9 and 1.27:
   ☐ is enclosed.
   ☐ was filed in prior application number _____ and such status is still proper and desired (37 C.F.R. § 1.28(a)).

3. ☒ The U.S. Patent and Trademark Office is hereby authorized to charge any fees that may be required under 37 C.F.R. §§ 1.16 and 1.17, or credit any overpayment, to Deposit Account No. 19-0036. A duplicate copy of this sheet is enclosed.

4. ☒ A check in the amount of $ 900.00 is enclosed to cover ($770.00) basic filing fee and ($130.00) petition fee;

(*REQUEST FOR FILING A PATENT APPLICATION UNDER 37 C.F.R. § 1.60, PAGE 2*)

5. ☒ Cancel in this application original claims 2-27 of the prior application before calculating the filing fee. (At least one original independent claim must be retained for filing purposes.)

6. ☒ The inventors of the invention being claimed in this application are: Jean Mesens, Michael E. Rickey, and Thomas J. Atkins.

7. ☐ This application is being filed by less than all the inventors named in the prior application. In accordance with 37 C.F.R. § 1.60(b), the Assistant Commissioner is requested to delete the name(s) of the following person or persons who are not inventors of the invention being claimed in this application:

8. ☒ Amend the specification by inserting before the first line the sentence:

This application is a ☒ continuation ☐ division of application no. 08/154,403, filed November 19, 1993, (status: pending).

9. ☐ New formal drawings are enclosed.

10. ☐ Priority of foreign application number _____, filed on _____ in _____ is claimed under 35 U.S.C. § 119(a)-(d).
☐ The certified copy has been filed in prior application number _____, filed _____.

11. ☒ A preliminary amendment is enclosed.

12. ☒ The prior application is assigned of record to Alkermes Controlled Therapeutics, Inc. II and Janssen Pharmaceutica.

13. ☒ Also enclosed: (1) Request for Interference Under 37 C.F.R. § 1.604; (2) Petition to Make Special Under 37 C.F.R. § 1.102(d) and Incorporated Information Disclosure Statement; (3) Form PTO-1449; and (4) 26 cited documents.

14. ☒ The power of attorney in the prior application is to Robert Greene Sterne, Edward J. Kessler, Jorge A. Goldstein, Samuel L. Fox, David K. S. Cornwell, Robert W. Esmond, Tracy-Gene G. Durkin, and Michele A. Cimbala, all of Sterne, Kessler, Goldstein & Fox (now Sterne, Kessler, Goldstein & Fox P.L.L.C.).
a.☒ The power of attorney appears in the original papers in the prior application.
b.☐ Since the power does not appear in the original papers, a copy of the power in the prior application is enclosed.

Address all future correspondence to: (May only be completed by applicant, attorney or agent of record.)

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
1100 New York Avenue, N.W., Suite 600
Washington, D.C. 20005-3934

February 28, 1997
Date

Andrea G. Reister
Registration No. 36,253

☐ inventor
☐ assignee of complete interest. Certification under 37 CFR § 3.73(b) is enclosed.
☐ attorney or agent of record
☒ filed under 37 C.F.R. § 1.34(a)

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Mesens *et al.*

Appl. No. To be assigned
(Continuation of 08/154,403)

Filed: Herewith

For: **Microencapsulated 3-Piperidynyl-Substituted 1,2-Benzisoxazoles and 1,2-Benzisothiazoles**

Art Unit: To be assigned

Examiner: To be assigned

Atty. Docket: 1611.0510002/AGR

Preliminary Amendment

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Please enter the following Preliminary Amendment in the application filed herewith prior to the examination thereof.

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 19-0036.

Amendments

In the Claims:

Please cancel claim 1. Claims 2-27 were canceled on the Division-Continuation Program Application Transmittal Form filed herewith. Please add the following new claims 28-30.

--28. A sustained-release microparticle comprising:

risperidone, or a pharmaceutically acceptable acid addition salt thereof, in crystalline form; and

a biodegradable and biocompatible polymeric matrix.

29. The sustained-release microparticle according to claim 28, wherein said polymeric matrix comprises a polymer selected from the group consisting of poly(lactic) acid, poly(glycolic) acid, copolymers of the foregoing, and polyorthoesters.

30. A sustained-release microparticle produced by including risperidone, or a pharmaceutically acceptable acid addition salt thereof, in the form of crystals into a biodegradable and biocompatible polymer selected from the group consisting of poly(lactic) acid, poly(glycolic) acid, copolymers of the foregoing, and polyorthoesters.--

In the Abstract:

Please delete the Abstract of the Disclosure as it appears on pages 46 and 47 of the application as filed herewith, and substitute therefor the Abstract attached hereto on a separate sheet.

Remarks

The above-captioned continuation application has been filed in order to request that an interference be declared with the U.S. national phase application of PCT/JP93/01673 that designated the United States (see Request for Interference Under 37 C.F.R. § 1.604 filed herewith). To facilitate processing by the PTO, it is requested that the above-captioned application be assigned to the same Examiner and Art Unit as the U.S. national phase application of PCT/JP93/01673.

Upon entry of the foregoing amendment, claims 28-30 are pending in the application, with claims 28 and 30 being the independent claims. Claims 1-27 are canceled without prejudice to or disclaimer of the subject matter therein. New claims 28-30 are added. These changes are believed to introduce no new matter, and their entry is respectfully requested. In this regard, the Examiner is referred to, for example, page 15, line 28 and page 20, line 26 of the above-referenced application that discloses use of an active agent in crystalline form, and page 25, lines 14-22 (Example 1) that discloses a method for producing risperidone in crystalline form.

Conclusion

Prompt and favorable consideration of this Preliminary Amendment is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Andrea G. Reister
Attorney for Applicants
Registration No. 36,253

Date: February 28, 1997

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SLF\AGR:daw

Abstract

A sustained-release microparticle comprising a 1,2 benzazole within a polymeric matrix. One sustained-release microparticle can be produced by including risperidone in the form of crystals into a biodegradable and biocompatible polymer, such as poly(lactic) acid, poly(glycolic) acid, and the copolymers of the foregoing. The sustained-release microparticles can be formulated in a liquid injection vehicle for administration to animals suffering from mental illness.

Microencapsulated 3-Piperidinyl-Substituted 1,2-Benzisoxazoles and 1,2-Benzisothiazoles

Background of the Invention

1. Field of the Invention

The present invention relates to microencapsulated 1,2-benzazoles and their use in the treatment of warm blooded animals suffering from mental illness More particularly, the present invention relates to microencapsulated 3-piperidinyl-substituted 1,2-benzisoxazoles and 1,2-benzisothiazoles and their use in the treatment of mental patients.

2. Description of the Related Art

Strupczewski *et al.*, in U.S. Patent No. 4,352,811 and U.S. Patent No. 4,458,076, describe 3-piperidinyl-1,2-benzisoxazoles and 3-piperidinyl-1,2-benzisothiazoles having antipsychotic and analgesic properties.

Kennis et al., U.S. Patent No. 4,804,663, disclose 3-piperidinyl-1,2-benzisothiazoles and 3-piperidinyl-1,2-benzisoxazoles and their pharmaceutically acceptable acid addition salts that have antipsychotic properties and are useful in the treatment of a variety of complaints in which serotonin release is of predominant importance. In particular, 3 – [2 – [4 – (6 – fluoro – 1,2 – benzisoxazol – 3 – yl) – 1 – piperidinyl) ethyl] – 6,7,8,9 - tetrahydro - 2 - methyl - 4H - pyrido[1,2 - a] pyrimidin - 4 - one ("Risperidone") is disclosed.

Janssen *et al.*, U.S. Patent No. 5,158,952, 3-piperidinyl-1,2-benzisoxazoles having long-acting antipsychotic properties and which are useful in the treatment of warm-blooded animals suffering from psychotic diseases. In particular, 3 – [2 – [4 – (6 – fluoro – 1,2 – benzisoxazol –

3 – yl) – 1 – piperidinyl) ethyl] – 6,7,8,9 - tetrahydro - 9 - hydroxy - 2 - methyl - 4H - pyrido[1,2 - a] pyrimidin - 4 - one ("9-hydroxy-Risperidone") is disclosed.

A number of methods are known by which compounds can be encapsulated in the form of microparticles. In many of these processes, the material to be encapsulated is dispersed in a solvent containing a wall forming material. At a single stage of the process, solvent is removed from the microparticles and thereafter the microparticle product is obtained.

An example of a conventional microencapsulation process and microparticles produced thereby is disclosed in U. S. Patent No. 3,737,337, incorporated by reference herein, wherein a solution of a wall or shell forming polymeric material in a solvent is prepared. The solvent is only partially miscible in water. A solid or core material is dissolved or dispersed in the polymer-containing solution and, thereafter, the core-material-containing solution is dispersed in an aqueous liquid that is immiscible in the organic solvent in order to remove solvent from the microparticles.

Another example of a process in which solvent is removed from microparticles containing a substance is disclosed in U. S. Patent No. 3,523,906. In this process a material to be encapsulated is emulsified in a solution of a polymeric material in a solvent that is immiscible in water and then the emulsion is emulsified in an aqueous solution containing a hydrophilic colloid. Solvent removal from the microparticles is then accomplished by evaporation and the product is obtained.

In still another process as shown in U. S. Patent No. 3,691,090 organic solvent is evaporated from a dispersion of microparticles in an aqueous medium, preferably under reduced pressure.

Similarly, the disclosure of U. S. Patent No. 3,891,570 shows a method in which solvent from a dispersion of microparticles in a polyhydric

alcohol medium is evaporated from the microparticles by the application of heat or by subjecting the microparticles to reduced pressure.

Another example of a solvent removal process is shown in U. S. Patent No. 3,960,757.

Tice *et al.*, in U. S. Patent No. 4,389,330, describe the preparation of microparticles containing an active agent - which may, *inter alia*, be a psychotherapeutic agent - by a method comprising: (a) dissolving or dispersing an active agent in a solvent and dissolving a wall forming material in that solvent; (b) dispersing the solvent containing the active agent and wall forming material in a continuous-phase processing medium; (c) evaporating a portion of the solvent from the dispersion of step (b), thereby forming microparticles containing the active agent in the suspension; and (d) extracting the remainder of the solvent from the microparticles.

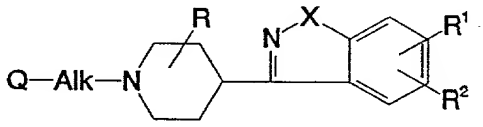
Tice *et al.*, in U. S. Patent No. 4,530,840, describe the preparation of microparticles containing an anti-inflammatory active agent by a method comprising: (a) dissolving or dispersing an anti-inflammatory agent in a solvent and dissolving a biocompatible and biodegradable wall forming material in that solvent; (b) dispersing the solvent containing the anti-inflammatory agent and wall forming material in a continuous-phase processing medium; (c) evaporating a portion of the solvent from the dispersion of step (b), thereby forming microparticles containing the anti-inflammatory agent in the suspension; and (d) extracting the remainder of the solvent from the microparticles.

Summary of the Invention

The present invention relates to microencapsulated 1,2-benzazoles and their use in the treatment of warm blooded animals suffering from mental disease. In a preferred embodiment, the invention relates to a

pharmaceutical composition designed for the controlled release of an effective amount of a drug over an extended period of time, prepared in microparticle form. This composition comprises at least one antipsychotic agent and at least one biocompatible, biodegradable encapsulating polymer.

More particularly, the present invention relates to a method of treating warm blooded animals suffering from psychotic disorders comprising the administration thereto of a pharmaceutically effective amount of a biodegradable and biocompatible microparticle composition comprising a 1,2-benzazole of the formula



(I)

and the pharmaceutically acceptable acid addition salts thereof, wherein

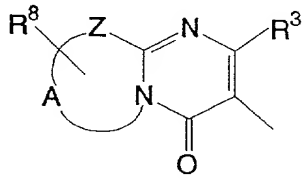
R is hydrogen or alkyl of 1 to 6 carbon atoms;

R^1 and R^2 are independently selected from the group consisting of hydrogen, halo, hydroxy, alkyloxy of 1 to 6 carbon atoms, and C alkyl of 1 to 6 carbon atoms;

X is O or S;

Alk is C_{1-4} alkanediyl; and

Q is a radical of formula



(a)

wherein

R^3 is hydrogen or alkyl of 1 to 6 carbon atoms;

Z is —S—, —CH_2—, or —CR^4=CR^5—; where R^4 and R^5 are independently selected from the group consisting of hydrogen or alkyl of 1 to 6 carbon atoms;

A is a bivalent radical —CH_2—CH_2—, —CH_2—CH_2—CH_2— or CR^6=CR^7—; where R^6 and R^7 are independently selected from the group consisting of hydrogen, halo, amino or alkyl of 1 to 6 carbon atoms; and

R^8 is hydrogen or hydroxyl;

within a polymeric matrix.

In another aspect, the present invention relates to a pharmaceutical composition comprising a biodegradable and biocompatible microparticle composition comprising a 1,2-benzazole of Formula I within a polymeric matrix.

In still another aspect, the present invention relates to a method of inhibiting serotonergic or dopaminergic overstimulation in animals wherein said method comprises administration of a biodegradable and biocompatible microparticle composition comprising a 1,2-benzazole of Formula I within a polymeric matrix.

Brief Description of the Drawings

Figure 1 shows a laboratory set-up for carrying out a preferred process for preparing the microparticles of the present invention;

Figure 2 depicts a graph of *in vitro* dissolution data for risperidone microparticles of batch Prodex 3, both as produced and lyophilized.

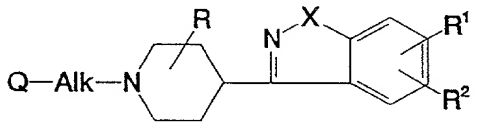
Figure 3 depicts a graph of *in vitro* dissolution data for risperidone microparticles of batch Prodex 2, both as produced and lyophilized.

Figure 4 depicts a graph of accelerated *in vitro* dissolution data for risperidone microparticles of batches Prodex 3 and Prodex 2.

Figure 5 depicts a graph of mean (n = 2) plasma concentration-time curves for the active moiety (sum of risperidone and 9-hydroxy risperidone) after single intramuscular administration to beagle dogs of risperidone depot formulations at an approximate dose of 2.5 mg/kg. The period of anti-emetic activity (in at least 2 out of 3 dogs) in the apomorphine vomiting test is given in the legend for each of the formulations. An asterisk (*) indicates that the anti-emetic activity is interrupted in at least 2 out of 3 dogs at the beginning of the study. The broken line indicates an approximate lowest minimum plasma concentration necessary for anti-emetic activity. The // sign indicates that for formulation Prodex 2 no blood was sampled on days 14, 18, and 21.

Description of the Preferred Embodiments

The present invention is concerned with microencapsulated 1,2-benzazoles having the formula



(I)

and the pharmaceutically acceptable acid addition salts thereof, wherein

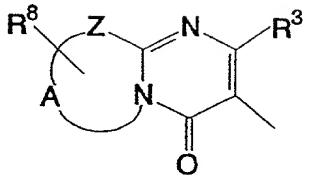
R is hydrogen or alkyl of 1 to 6 carbon atoms;

R^1 and R^2 are independently selected from the group consisting of hydrogen, halo, hydroxy, alkyloxy of 1 to 6 carbon atoms and alkyl of 1 to 6 carbon atoms;

X is O or S;

Alk is alkanediyl of 1 to 4 carbon atoms; and

Q is a radical of formula



(a)

wherein

R^3 is hydrogen or alkyl of 1 to 6 carbon atoms;

Z is —S—, —CH_2—, or —CR^4=CR^5—; where R^4 and R^5 are independently selected from the group consisting of hydrogen or alkyl of 1 to 6 carbon atoms;

A is a bivalent radical —CH_2—CH_2—, —CH_2—CH_2—CH_2— or CR^6=CR^7—; where R^6 and R^7 are independently selected from the group consisting of hydrogen, halo, amino, or alkyl of 1 to 6 carbon atoms; and

R^8 is hydrogen or hydroxyl.

In the foregoing definitions, the term "halo" is generic to fluoro, chloro, bromo, and iodo; "alkyl of 1 to 6 carbon atoms" is meant to include straight and branched chain saturated hydrocarbon radicals having from 1 to 6 carbon atoms, such as, for example, methyl, ethyl, propyl, butyl, pentyl, hexyl, and isomers thereof; "alkanediyl of 1 to 4 carbon atoms" is meant to include bivalent straight or branched chain alkanediyl radicals having from 1 to 4 carbon atoms, such as, for example, methylene, ethylene, propylene, butylene, and isomers thereof.

Preferred compounds within the invention are those wherein Q is a radical of formula (a) wherein R^3 is alkyl of 1 to 6 carbon atoms and A is a bivalent radical —CH_2-CH_2—, —CH_2—CH_2—CH_2—, or —CR^6=CR^7—, wherein R^6 and R^7 are independently selected from the group consisting of hydrogen and alkyl of 1 to 6 carbon atoms.

Particularly preferred compounds are those wherein Q is a radical of formula (a) wherein R^3 is alkyl of 1 to 6 carbon atoms and A is a bivalent radical $—CH_2-CH_2—$, $—CH_2—CH_2—CH_2—$, or $—CR^6=CR^7—$, wherein R^6 and R^7 are independently selected from the group consisting of hydrogen and alkyl of 1 to 6 carbon atoms, R is hydrogen, R^1 is hydrogen or halo, and R^2 is hydrogen, halo, hydroxy, or alkyloxy of 1 to 6 carbon atoms.

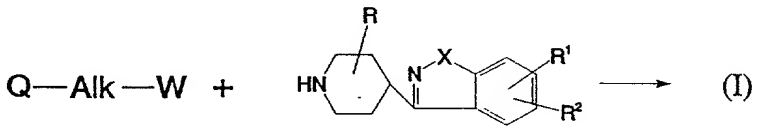
More particularly preferred compounds are those wherein R is hydrogen, R^1 is hydrogen or halo, and R^2 is hydrogen, halo, hydroxy, or alkyloxy of 1 to 6 carbon atoms and Q is a radical of formula (a) wherein —Z—A— is $—CH_2—CH_2—CH_2—CH_2—$, $—S—CH_2—CH_2—$, $—S—(CH_2)_3—$, $—S—CR^6=CR^7—$, or $—CH=CH—CR^6=CR^7—$, wherein R^6 and R^7 are independently selected from the group consisting of hydrogen or methyl;

Especially preferred compounds are those compounds wherein R is hydrogen, R^1 is hydrogen, and R^2 is hydrogen, halo, hydroxy, or methoxy and Q is a radical of formula (a) wherein —Z—A— is $—CH_2—CH_2—CH_2—CH_2—$, $—S—CH_2—CH_2—$, $—S—(CH_2)_3—$, $—S—CR^6=CR^7—$, or $—CH=CH—CR^6=CR^7—$, wherein R^6 and R^7 are independently selected from the group consisting of hydrogen or methyl.

The most preferred compounds are selected from the group consisting of 3 - [2 - [4 - (6 - fluoro - 1,2 - benzisoxazol - 3 - yl) - 1 - piperidinyl) ethyl] - 6,7,8,9 - tetrahydro - 2 - methyl - 4H - pyrido[1,2 - a] pyrimidin - 4 - one ("Risperidone") and the pharmaceutically acceptable acid addition salts thereof.

The compounds of formula (I) can generally be prepared by the methods described in U.S. Patent No. 4,804,663, incorporated herein by reference. These methods comprise reacting an appropriate reactive ester of formula (II) with an appropriately substituted piperidine of formula (III). In the reactive ester (II), W represents a reactive ester moiety such as, for

example, halo, e.g., chloro, bromo, or iodo, or a sulfonyloxy group, e.g. methylsulfonyloxy, (4-methylphenyl)sulfonyloxy, and the like.



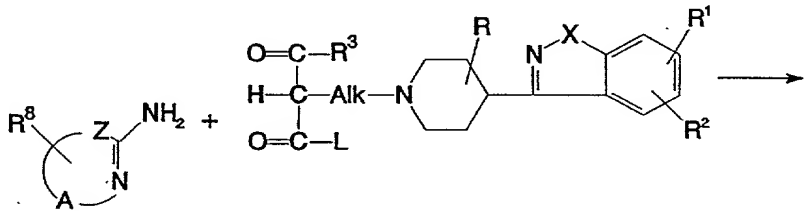
II III

The reaction of (II) with (III) can conveniently be conducted in an inert organic solvent such as, for example, an aromatic hydrocarbon, e.g., benzene, toluene, xylene, and the like; a lower alkanol, e.g., methanol, ethanol, propanol, butanol and isomers thereof; a ketone, e.g., acetone, 4-methyl-2-pentanone and the like; an ether, e.g., 1,4-dioxane, 1,1′-oxybisethane, tetrahydrofuran and the like; N,N-dimethylformamide (DMF); N,N-dimethylacetamide (DMA); nitrobenzene; 1-methyl-2-pyrrolidinone; and the like. The addition of an appropriate base such as, for example, an alkali or an alkaline earth metal carbonate, bicarbonate, hydroxide, alkoxide, or hydride, e.g., sodium carbonate, sodium bicarbonate, potassium carbonate, sodium hydroxide, sodium methoxide, sodium hydride, and the like, or an organic base such as, for example, a tertiary amine, e.g., N,N-diethylethanamine, N-(1-methylethyl)-2-propanamine, 4-ethylmorpholine, and the like can be used to neutralize the acid liberated during the course of the reaction. In some circumstances, the addition of an iodide salt, preferably an alkali metal iodide, is appropriate. Moderately elevated temperatures can be used to enhance the rate of the reaction.

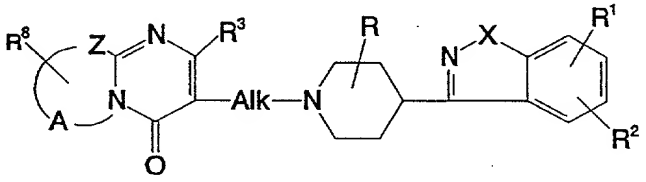
The compounds of formula (I) can also be prepared following art-known procedures for preparing compounds containing radicals of formula Q within their structure.

The compounds of formula (I) wherein Q is a radical of formula (a), said compounds being represented by the formula (I-a), can be prepared

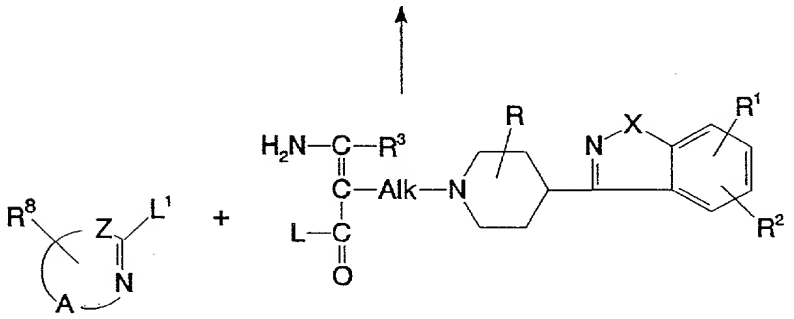
following art-known cyclizing procedures for preparing pyrimidin-4-ones, such as, for example, by reacting an amine of formula (VI) with a cyclizing agent of formula (VII) or by cyclizing a reagent of formula (VIII) with an amine of formula (IX).



(VI) (VII)



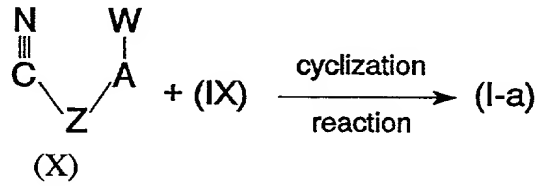
(I-a)



(VIII) (IX)

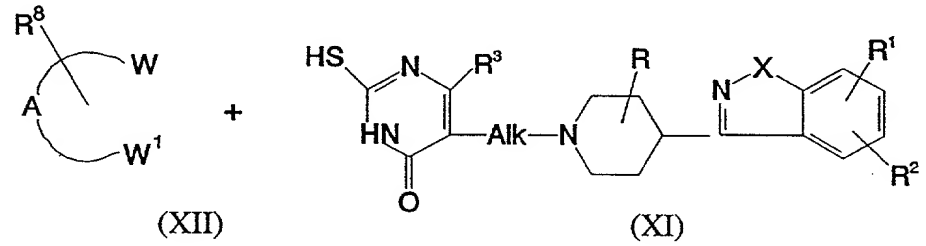
In the foregoing reaction schemes, L and L^1 each independently represent an appropriate leaving group such as, for example, (C_{1-6} alkyl)oxy, hydroxy, halo, amino, mono- and di(C_{1-6} alkyl)amino, and the like.

Following the same cyclization procedure the compounds of formula (I-a) can also be prepared by cyclizing an intermediate of formula (IX) with a reagent of formula (X).

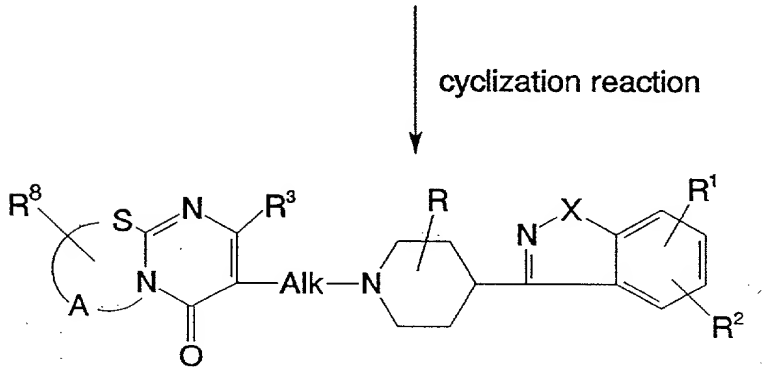


(X)

The compounds of formula (I-a) wherein Z is S, said compounds being represented by the formula (I-a-1), can also be prepared by cyclizing a 2-mercaptopyrimidinone of formula (XI) with a reagent of formula (XII).

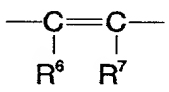


(XII) (XI)

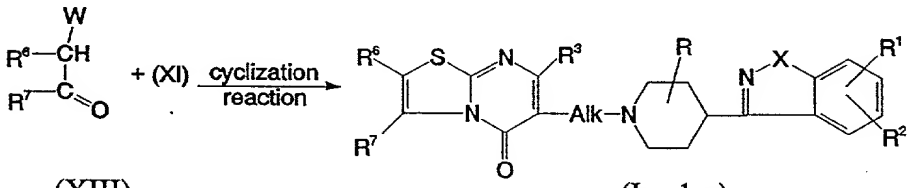


(I-a-1)

In (XII), W^1 has the same meaning as previously described for W. The compounds of formula (I-a-1) wherein A is



said compounds being represented by the formula (I-a-1-a), can also be prepared by cyclizing a 2-mercaptopyrimidinone of formula (XI) with a reagent of formula (XIII).



(XIII) (I-a-1-a)

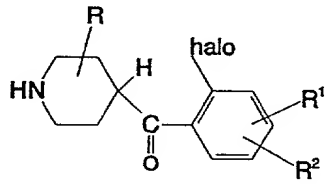
The cyclization reactions described above can be carried out as described above.

The compounds of formula (I) have basic properties and, consequently, can be converted to their therapeutically active non-toxic acid addition salt forms by treatment with appropriate acids, such as, for example, inorganic acids, such as hydrohalic acid, e.g., hydrochloric, hydrobromic, and the like; sulfuric acid, nitric acid, phosphoric acid, and the like; or organic acids, such as, for example, acetic, propanoic, hydroacetic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic,

toluenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic, and the like acids. Conversely the salt form can be converted by treatment with alkali into the free base form.

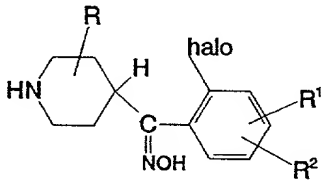
A number of intermediates and starting materials in the foregoing preparations are known compounds that can be prepared according to art-known methodologies. For example, the intermediates of formula (III) and their preparations are described in U.S. Patent Nos. 4,335,127; 4,342,870; 4,443,451; and 4,485,107.

The intermediates of formula (III) can generally be derived from a benzoylpiperidine of formula



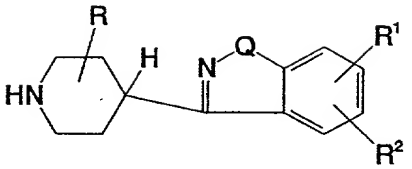
(XIV)

wherein halo is preferably fluoro, following art-known procedures, e.g., by reacting the benzoylpiperidine (XIV) with hydroxylamine and cyclizing the thus obtained oxime



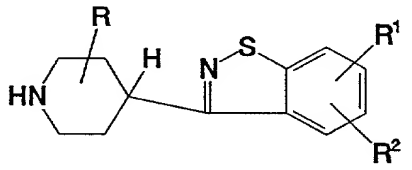
(XV)

following art known procedures, thus obtaining the intermediate of formula (III) wherein X is O, said intermediates being represented by the formula



(III-a)

The intermediates of formula (III) wherein X is S, said intermediates being represented by the formula



(III-b)

can be prepared following a procedure analogous to that described in U.S. Patent No. 4,458,076.

The compounds of formula (I) and the pharmaceutically acceptable acid addition salts thereof are potent antagonists of a series of neurotransmitters and, as a result, have useful pharmacological properties. In particular, the compounds of formula (I) and their pharmaceutically acceptable acid addition salts possess strong psychotic activity and antiserotonin activity.

Janssen *et al.* *(The Journal of Pharmacology and Experimental Therapeutics 244 (2)*:685-693 (1988)) made comparative studies of risperidone with ritanserin, a selective centrally acting serotonin-S_2 antagonist and with haloperidol, a selective centrally acting dopamine-D_2 antagonist. They reported that risperidone, like ritanserin, showed activity in all tests related to serotonin-S_2 antagonism, but at even lower doses. Like haloperidol, risperidone also showed activity in all tests related to dopamine-D_2 antagonism. They concluded that, qualitatively, risperidone is a mixed serotonin-dopamine antagonist.

Owing to their pharmacological activities, the compounds of formula (I) and their pharmaceutically acceptable acid addition salts are used in the

treatment of psychotic diseases and in the treatment of a variety of complaints in which serotonin release is of predominant importance such as, for example, in the blocking of serotonin-induced contractions of bronchial tissues and of blood vessels, arteries as well as veins. The subject compounds are also useful as sedating, anxiolytic, anti-aggressive, anti-stress, muscular protectant, and cardiovascular protectant agents and, consequently, are useful for protecting warm-blooded animals, for example, in stress situations. Additionally, these compounds are useful for protection against endotoxine shocks and as antidiarrheals.

In view of the usefulness of the subject compounds in the treatment of psychotic diseases, it is evident that the present invention provides a method of treating warm-blooded animals suffering from psychotic disorders, said method comprising the systemic administration of a pharmaceutically effective amount of a microencapsulated compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof in admixture with a pharmaceutical carrier. In general, it is contemplated that an effective amount of the compound, *per se*, would be from 0.01 mg/kg to 4 mg/kg body weight, more preferably, from 0.04 mg/kg to 2 mg/kg body weight.

In order to provide a clear and consistent understanding of the specification and claims, including the scope to be given such terms, the following definitions are provided.

By the term "administered" is intended any method of delivering the 1,2-benzazole-containing microparticles of the invention to a warm blooded animal, such as, for example, parenteral (intravenous, intramuscular, or subcutaneous) administration.

By "microparticles" is meant solid particles that contain an active agent, herein the 1,2-benzazole, either in solution or in crystalline form. The active agent is dispersed or dissolved within the polymer that serves as the matrix of the particle.

The present invention concerns a method of treating mental illness in warm blooded animals, preferably mammals, more preferably humans, (hereinafter, collectively referred to as "patients") that comprises providing to such patients biodegradable microparticles loaded with a 1,2-benzazole, as described above. The method of the present invention provides advantages over methods known in the art, such as, *inter alia*, a biodegradable system, an injectable system that prevents the loss of dose during treatment, the ability to mix microparticles containing different drugs, and the ability to program release (multiphasic release patterns) to give faster or slower rates of drug release as needed.

The product of the present invention offers the advantage of durations of action ranging from 7 to more than 200 days, depending upon the type of microparticle selected. In a preferred embodiment, the microparticles are designed to afford treatment to patients over a period of 30 to 60 days. The duration of action can be controlled by manipulation of the polymer composition, polymer:drug ratio, and microparticle size.

Another important advantage of the present invention is that practically all of the active agent is delivered to the patient because the polymer used in the method of the invention is biodegradable, thereby permitting all of the entrapped agent to be released into the patient.

A method for preparing the microparticles of the invention is also described in both U.S. 4,389,330 and U.S. 4,530,840, fully incorporated herein by reference.

The polymeric matrix material of the microparticles of the present invention is a biocompatible and biodegradable polymeric material. The term"biocompatible" is defined as a polymeric material that is not toxic to the human body, is not carcinogenic, and does not significantly induce inflammation in body tissues. The matrix material should be biodegradable in the sense that the polymeric material should degrade by bodily processes to products readily disposable by the body and should not accumulate in the

body. The products of the biodegradation should also be biocompatible with the body in the same sense that the polymeric matrix is biocompatible with the body. Suitable examples of polymeric matrix materials include poly(glycolic acid), poly-D,L-lactic acid, poly-L-lactic acid, copolymers of the foregoing, poly(aliphatic carboxylic acids), copolyoxalates, polycaprolactone, polydioxonone, poly(ortho carbonates), poly(acetals), poly(lactic acid-caprolactone), polyorthoesters, poly(glycolic acid-caprolactone), polyanhydrides, and natural polymers including albumin, casein, and waxes, such as, glycerol mono- and distearate,and the like. The preferred polymer for use in the practice of this invention is dl(polylactide-co-glycolide). It is preferred that the molar ratio of lactide to glycolide in such a copolymer be in the range of from about 75:25 to 50:50.

In a preferred embodiment, administration of the 1,2-benzazoles to patients by the method of the invention is achieved by a single administration of the drug loaded microparticles, releasing the drug in a constant or pulsed manner into the patient and eliminating the need for repetitive injections.

The formulation of the present invention contains an antipsychotic agent dispersed in a microparticle matrix material. The amount of agent incorporated in the microparticles usually ranges from about 1 wt % to about 90 wt. %, preferably 30 to 50 wt. %, more preferably 35 to 40 wt.%. By weight % is meant parts of agent per total weight of microparticle. For example, 10 wt. % agent would mean 10 parts agent and 90 parts polymer by weight.

The molecular weight of the polymeric matrix material is of some importance. The molecular weight should be high enough to permit the formation of satisfactory polymer coatings, i.e., the polymer should be a good film former. Usually, a satisfactory molecular weight is in the range of 5,000 to 500,000 daltons, preferably about 150,000 daltons. However,

since the properties of the film are also partially dependent on the particular polymeric material being used, it is very difficult to specify an appropriate molecular weight range for all polymers. The molecular weight of a polymer is also important from the point of view of its influence upon the biodegradation rate of the polymer. For a diffusional mechanism of drug release, the polymer should remain intact until all of the drug is released form the microparticles and then degrade. The drug can also be released from the microparticles as the polymeric excipient bioerodes. By an appropriate selection of polymeric materials a microparticle formulation can be made in which the resulting microparticles exhibit both diffusional release and biodegradation release properties. This is useful in affording multiphasic release patterns.

The microparticle product of the present invention can be prepared by any method capable of producing microparticles in a size range acceptable for use in an injectable composition. One preferred method of preparation is that described in U.S. 4,389,330. In this method the active agent is dissolved or dispersed in an appropriate solvent. To the agent-containing medium is added the polymeric matrix material in an amount relative to the active ingredient that provides a product having the desired loading of active agent. Optionally, all of the ingredients of the microparticle product can be blended in the solvent medium together.

Solvents for the agent and the polymeric matrix material that can be employed in the practice of the present invention include organic solvents, such as acetone; halogenated hydrocarbons, such as chloroform, methylene chloride, and the like; aromatic hydrocarbon compounds; halogenated aromatic hydrocarbon compounds; cyclic ethers; alcohols, such as, benzyl alcohol; ethyl acetate; and the like. A preferred solvent for use in the practice of the present invention is a mixture of benzyl alcohol and ethyl acetate.

The mixture of ingredients in the solvent is emulsified in a continuous-phase processing medium; the continuous-phase medium being such that a dispersion of microdroplets containing the indicated ingredients is formed in the continuous-phase medium. Naturally, the continuous-phase processing medium and the organic phase must be largely immiscible. The continuous-phase processing medium most commonly employed is water, although nonaqueous media, such as, xylene, toluene, and synthetic and natural oils can be used. Usually, a surfactant is added to the continuous-phase processing medium to prevent the microparticles from agglomerating and to control the size of the solvent microdroplets in the emulsion. A preferred surfactant-dispersing medium combination is a 0.1 to 10 wt. %, more preferably 0.5 to 2 wt. % solution of poly(vinyl alcohol) in water. The dispersion is formed by mechanical agitation of the mixed materials. An emulsion can also be formed by adding small drops of the active agent-wall forming material solution to the continuous phase processing medium. The temperature during the formation of the emulsion is not especially critical, but can influence the size and quality of the microparticles and the solubility of the agent in the continuous phase. Of course, it is desirable to have as little of the agent in the continuous phase as possible. Moreover, depending on the solvent and continuous-phase processing medium employed, the temperature must not be too low or the solvent and processing medium will solidify or become too viscous for practical purposes. On the other hand, it must not be so high that the processing medium will evaporate or that the liquid processing medium will not be maintained. Moreover, the temperature of the medium cannot be so high that the stability of the particular active agent being incorporated in the microparticles is adversely affected. Accordingly, the dispersion process can be conducted at any temperature that maintains stable operating conditions, preferably about 20°C to about 60°C, depending upon the agent and excipient selected.

The dispersion formed is stable and from this dispersion the organic phase fluid can be partially removed in the first step of the solvent removal process. The solvent can easily be removed by common techniques, such as heating, the application of a reduced pressure, or a combination of both. The temperature employed to evaporate solvent from the microdroplets is not critical, but should not be so high as to degrade the agent employed in the preparation of a given microparticle or to evaporate solvent at a rate rapid enough to cause defects in the wall forming material. Generally, from 10 to 90%, preferably 40 to 60% of the solvent is removed in the first solvent removal step.

After the first stage, the dispersed microparticles in the solvent immiscible fluid medium are isolated from the fluid medium by any convenient means of separation. Thus, for example, the fluid can be decanted from the microparticles or the microparticle suspension can be filtered. Various other combinations of separation techniques can be used, if desired.

Following the isolation of the microparticles from the continuous-phase processing medium, the remainder of the solvent in the microparticles is removed by extraction. In this step, the microparticles can be suspended in the same continuous-phase processing medium used in step one, with or without surfactant, or in another liquid. The extraction medium removes the solvent from the microparticles, but does not dissolve them. During the extraction, the extraction medium containing dissolved solvent must be removed and replaced with fresh extraction medium. This is best done on a continual or continuous basis where the rate of extraction medium replenishment is critical. If the rate is too slow, agent crystals may protrude from the microparticles or grow in the extraction medium. Obviously, the rate of extraction medium replenishment for a given process is a variable that can easily be determined at the time the process is performed and, therefore, no precise limits for the rate may be

predetermined. After the remainder of the solvent has been removed, the microparticles are dried by exposure to air or by other conventional drying techniques, such as, vacuum drying, drying over a desiccant, or the like. This process is very efficient in encapsulating the agent since core loadings of up to 80 wt. %, preferably up to 50 wt. % can be obtained.

A more preferred method of encapsulating the active agent to form the controlled release microparticles of the present invention involves the use of static mixers, in the method disclosed by our co-worker, Paul F. Herbert, in co-pending U.S. Patent Application Serial No. _____, filed of even date herewith.

Static or motionless mixers consist of a conduit or tube in which is received a number of static mixing elements. Static mixers provide homogeneous mixing in a relatively short length of conduit, and in a relatively short period of time. With static mixers, the fluid moves through the mixer, rather than some part of the mixer, such as a blade, moving through the fluid. A static mixer is more fully described in U.S. Patent No. 4,511,258, which is incorporated herein by reference.

When using a static mixer to form an emulsion, a variety of factors determine emulsion particle size. These factors include the density and viscosity of the various solutions or phases to be mixed, volume ratio of the phases, interfacial tension between the phases, static mixer parameters (conduit diameter; length of mixing element; number of mixing elements), and linear velocity through the static mixer. Temperature is a variable because it affects density, viscosity, and interfacial tension. The controlling variables are linear velocity, shear rate, and pressure drop per unit length of static mixer. Particularly, droplet size decreases as linear velocity increases and droplet size increases as pressure drop decreases. Droplets will reach an equilibrium size after a fixed number of elements for a given flow rate. The higher the flow rate, the fewer elements needed. Because of these relationships, scaling from laboratory batch sizes to commercial

batch sizes is reliable and accurate, and the same equipment can be used for laboratory and commercial batch sizes.

In order to create microparticles containing an active agent, an organic phase and an aqueous phase are combined. The organic and aqueous phases are largely or substantially immiscible, with the aqueous phase constituting the continuous phase of the emulsion. The organic phase includes an active agent as well as a wall forming polymer or polymeric matrix material. The organic phase can be prepared by dissolving an active agent in an organic or other suitable solvent, or by forming a dispersion or an emulsion containing the active agent. In the more preferred process used in the practice of the present invention, the organic phase and the aqueous phase are pumped so that the two phases are simultaneously flowing through a static mixer, thereby forming an emulsion, which comprises microparticles containing the active agent encapsulated in the polymeric matrix material. The organic and aqueous phases are pumped through the static mixer into a large volume of quench liquid. The quench liquid may be plain water, a water solution, or other suitable liquid. Organic solvent may be removed from the microparticles while they are being washed or being stirred in the quench liquid. After the microparticles are washed in a quench to extract or remove the organic solvent, they are isolated, as through a sieve, and dried.

A laboratory set up for carrying out a static mixer process is illustrated in Figure 1. An organic or oil phase **30** is prepared by dissolving and, optionally, heating an active agent and a polymeric matrix material or polymer in a stirred pot **32** on a hot plate. However, the process of the present invention is not limited to preparing organic phase **30** by dissolving an active agent. Alternatively, organic phase **30** may be prepared by dispersing an active agent in a solution containing a polymeric matrix material. In such a dispersion, the active agent is only slightly soluble in organic phase **30**. Alternatively, organic phase **30** may be

prepared by preparing an emulsion containing an active agent and a polymeric matrix material (double emulsion process). In the double emulsion process, a primary emulsion is prepared which contains an active agent and a polymeric matrix material (organic phase **30**). The primary emulsion may be a water-in-oil emulsion, an oil-in-water emulsion, or any suitable emulsion. The primary emulsion (organic phase **30**) and an aqueous phase are then pumped through a static mixer to form a second emulsion which comprises microparticles containing the active agent encapsulated in the polymeric matrix material.

Organic phase **30** is pumped out of stirred pot **32** by a magnetically driven gear pump **34**. The discharge of pump **34** feeds a "Y" connection **36**. One branch **361** of "Y" connection **36** returns to pot **32** for recirculation flow. The other branch **362** feeds into an in-line static mixer **10**. Aqueous or water phase **40** is prepared in like manner, with a stirred pot **42**, a magnetically driven gear pump **44**, and a "Y" connection **46**. One branch **461** of "Y" connection **46** returns to pot **42** for recirculation flow. The other branch **462** feeds into in-line static mixer **10**. Organic phase **30** and aqueous phase **40** are substantially immiscible.

Branches **362** and **462** from each solution which feed in-line static mixer **10** are joined by another "Y" connection **50** and feed through mixer inlet line **51** into static mixer **10**. Static mixer **10** discharges through mixer outlet line **52** into wash tank **60**. Silicone tubing and polypropylene fittings are used in the system illustrated in Figure 1. Silicone tubing having 3/8 inch ID is used for all lines except mixer outlet line **52**. Smaller diameter tubing (3/16 inch ID) is used for mixer outlet line **52** to prevent collapse of the emulsion both in mixer outlet line **52** and upon entering wash tank **60**.

In one embodiment of the process, pumps **34** and **44** are started in recirculation mode and desired flow rates are set for organic phase **30** and water phase **40**. The flow rate of water phase **40** is preferably greater than

the flow rate of organic phase **30**. However, the two flow rates may be substantially the same. The ratio of the flow rate of water phase **40** to the flow rate of organic phase **30** is preferably in the range of 1:1 to 10:1. "Y" connection **46** is then switched so that water phase **40** flows through branch **462** to static mixer **10**. Once water phase **40** fills mixer inlet line **51**, static mixer **10**, and mixer outlet line **52**, "Y" connection **36** is switched so that organic phase **30** flows through branch **362** to static mixer **10**. Organic phase **30** and aqueous phase **40** are now flowing simultaneously through static mixer **10**. When the desired volume of organic phase has been pumped to static mixer **10**, "Y" connection **36** is switched to recirculation through branch **361**. Water phase **40** continues to flow for a short time to clean out any organic phase remaining in mixer inlet line **51**, static mixer **10**, and mixer outlet line **52**. "Y" connection **46** is then switched to recirculation through branch **461**.

Organic phase **30** and aqueous phase **40** are mixed in static mixer **10** to form an emulsion. The emulsion formed comprises microparticles containing the active agent encapsulated in the polymeric matrix material. The microparticles produced by the method of the present invention are usually of a spherical shape, although they may be irregularly shaped. The microparticles produced by the method of the present invention can vary in size, ranging from submicron to millimeter diameters. In a preferred embodiment of the present invention, static mixing elements **14** of static mixer **10** are selected so that the resulting microparticles range in size from 1 to 500 microns (μm), more preferably 25 to 180 microns, whereby administration of the microparticles can be carried out with a standard gauge needle. The microparticles may be stirred in wash tank **60** which contains a quench liquid. The microparticles may be isolated from the quench liquid, such as by using a sieve column. The microparticles may be dried using conventional drying techniques, and further size isolation may be done.

The active agent bearing microparticles are obtained and stored as a dry material. Prior to administration to a patient, the dry microparticles can be suspended in an acceptable pharmaceutical liquid vehicle, preferably a 2.5 wt. % solution of carboxymethyl cellulose, whereupon the suspension is injected into the desired portion of the body.

The microparticles can be mixed by size or by type so as to provide for the delivery of active agent to the patient in a multiphasic manner and/or in a manner that provides different agents to the patient at different times, or a mixture of agents at the same time.

The following examples further describe the materials and methods used in carrying out the invention. The examples are not intended to limit the invention in any manner.

Example 1

A mixture of 5.3 parts of 3-(2-chloromethyl)-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one monohydrochloride, 4.4 parts of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole, 8 parts of sodium carbonate, 0.1 part of potassium iodide, and 90 parts of DMF is stirred overnight at 80°-90° C. After cooling, the reaction mixture is poured into water. The product is filtered off and crystallized from a mixture of DMF and 2-propanol. The product is filtered off and dried, yielding 3.8 parts (46%) of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one; mp. 170.0° C.

Example 2: Preparation of 35% Theoretically Loaded Risperidone Microparticles (Batch Prodex 2)

First, the aqueous phase (solution A) is prepared by weighing and mixing 906.1 g 1% poly(vinyl alcohol), (Vinyl 205, Air Products and

Chemical Inc., Allentown, PA), 29.7 g benzyl alcohol (J.T. Baker, Phillipsburg, N.J.) end 65.3 g ethyl acetate (Fisher Scientific, Fair Lawn, N.J.). Then the organic phase (solution B) is prepared by dissolving 29.3 g of high viscosity 75:25 dl (polylactide-co-glycolide), (commercially available from Medisorb Technologies International, L.P., Cincinnati, OH) in 108.7 g ethyl acetate and 108.4 g benzyl alcohol. Once the polymer is completely dissolved, 15.7 g risperidone base (Janssen Pharmaceutica, Beerse, Belgium) is added and dissolved in the polymer solution. The exposure time of the dissolved risperidone with the polymer is kept to a minimum (< 10 minutes). Solutions A and B are then pumped through a 1/4 inch diameter static mixer (Cole Parmer L04667-14) via a gear drive pump and head (Cole Parmer L07149-04, L07002-16) at flow rates of 198 and 24 ml/minute, respectively, into a quench composed of 55 liters of water for injection containing 1276.0 g of ethyl acetate, 92.3 g (0.02 Molar) of anhydrous sodium bicarbonate, and 116.2 g (0.02 Molar) of anhydrous sodium carbonate (Mallinckrodt Specialty Chemicals, Paris, KY) at 11°C. The microparticles are allowed to stir in the first wash for 1.75 hours, then isolated by sieving with a 25-micron sieve. The product retained by the sieve is transferred to a 20-liter wash at 13°C. After stirring in the sieved wash for 2.25 hours, the microparticles are isolated and size fractionated by sieving through a stainless steel sieve column composed of 25- and 180-micron mesh sizes. The microparticles are dried overnight, then collected and weighed.

Example 3: Preparation of 40% Theoretically Loaded Risperidone Microparticles (Batch Prodex 3)

First, the aqueous phase (solution A) is prepared by weighing and mixing 904.4 g 1% poly (vinyl alcohol), (Vinyl 205, Air Products and Chemical Inc., Allentown, PA), 30.1 g benzyl alcohol (J.T. Baker,

Phillipsburg, N.J.) and 65.8 g ethyl acetate (Fisher Scientific, Fair Lawn, N.J.). Then the organic phase (solution B) is prepared by dissolving 27.1 g of high viscosity 75:25 dl (polylactide-co-glycolide), (Medisorb Technologies International, L.P., Cincinnati, OH) in 99.3 g ethyl acetate and 99.1 g benzyl alcohol. Once the polymer is completely dissolved, 18.1 g risperidone base (Janssen Pharmaceutica, Beerse, Belgium) is added and dissolved in the polymer solution. The exposure time of the dissolved risperidone with the polymer is kept to a minimum (< 10 minutes). Solutions A and B are then pumped through a 1/4 inch diameter static mixer (Cole Parmer L04667-14) via a gear drive pump and head (Cole Parmer L07149-04, L07002-16) at flow rates of 198 and 24 ml/minute, respectively, and into a quench composed of 55 liters of water for injection containing 1375.6 g of ethyl acetate, 92.4 g (0.02 Molar) of anhydrous sodium bicarbonate, and 116.6 g (0.02 Molar) of anhydrous sodium carbonate (Mallinckrodt Specialty Chemicals, Paris, KY) at 12°C. The microparticles are allowed to stir in the first wash for 2 hours, then isolated by sieving with a 25-micron sieve. The product retained by the sieve is transferred to a 20-liter wash at 12°C. After stirring in the sieved wash for 3 hours, the microparticles are isolated and size fractionated by sieving through a stainless-steel sieve column composed of 25- and 180-micron mesh sizes. The microparticles are dried overnight, then collected and weighed.

Example 4: Lyophilization and Gamma Irradiation of Microparticles from Batches Prodex 2 and Prodex 3 (Samples Prodex 4A, Prodex 4B, and Prodex 4C)

Microparticles from batches Prodex 2 and Prodex 3 were lyophilized. The microparticles were weighed into 5 cc serum vials. Then an aqueous vehicle composed of 0.75% CMC, 5% Mannitol, and 0.1% Tween 80 was added to the vials. The microparticles were suspended in

the vehicle by agitation, then quickly frozen in a dry ice/acetone bath. The vials were then lyophilized in a pilot-scale lyophilizer (Dura Stop Microprocessor Control, FTS Systems, Inc., Stone Ridge, N.Y.) employing a ramped 30°C maximum temperature cycle for 50 hours. Samples Prodex 4A and Prodex 4C were lyophilized samples from Prodex 2 and Prodex 3, respectively. Sample Prodex 4B was lyophilized from Prodex 2 that had been subsequently sterilized by 2.2 MRad gamma irradiation from a ^{60}Co source.

In Vitro Dissolution Studies

In vitro dissolution studies were conducted on Prodex 2, Prodex 3, Prodex 4A, Prodex 4B, and Prodex 4C. Real time and accelerated methodologies were used. The equipment consisted of a Hanson research 6-cell USP paddle (Method II) dissolution apparatus interfaced with a spectrophotometer and data station. Receiving media were continuously recirculated from each cell to flow cells inside the spectrophotometer (absorbance maximum of 236nm).

The real time model measured the release rates of microparticles into a receiving medium consisting of 50mM tris buffer at pH 7.4 at 37°C. Risperidone was found to have sufficient solubility ($\geq$0.5mg/ml) to allow *in vitro* experiments with this receiving medium. The amount of risperidone was kept below 20% of saturation to provide infinite sink conditions. Data are shown in Figures 2 and 3.

An accelerated model was also developed. A receiving medium of 27.5 wt% ethanol was used. Results are shown in Figure 4.

Animal Dosing and Blood Sampling

In vivo studies in dogs were conducted on product provided as dry microparticles (Prodex 2, Prodex 3) and in lyophilized form (Prodex 4A, Prodex 4B, Prodex 4C). The dry microparticles were syringe-loaded and resuspended in the syringe with an injection vehicle comprised of 2.5 wt% carboxymethyl cellulose (CMC). The lyophilized samples (Prodex 4A, Prodex 4B, Prodex 4C) were reconstituted in WFI (water for injection) prior to injection.

Male and female dogs, weighing 11.6 $\pm$2.3 kg, were divided into groups of three dogs each. The dogs were housed in groups of three and fed according to standard laboratory conditions.

The appropriate volumes of the respective depot formulations were dosed intramuscularly into the biceps femoralis of the left hind limb at the level of the thigh of the dogs at a dose of approximately 2.5 mg/kg risperidone.

Blood samples (5 ml on EDTA) were taken from one of the jugular veins at 0 (predose), 1, 5, and 24 hours after dosing and also on days 4, 7, 11, 14, 18, 23, 25, 28, 32, 35, 39, 42, 46, 49, 53, and 56 at the time of the apomorphine vomiting test. The apomorphine test was described by P.A.J. Janssen and C.J.E. Niemegeers in *Arzneim.-Forsch. (Drug Res.), 9*:765-767 (1959). If, during the course of the experiments, each of the three dogs of a group no longer showed protection against apomorphine-induced vomiting, blood sampling was discontinued. Blood samples were centrifuged at 3000 rpm for 10 min and plasma was separated. The plasma samples were stored at $\leq$20°C until analysis.

Plasma samples were analyzed for risperidone (RISP) and for 9-hydroxyrisperidone (9-OH RISP) using radioimmunoassay (RIA). For the plasma samples analyzed with RIA, two different RIA procedures were used, one for unchanged risperidone and the other for the active moiety

(sum of risperidone and 9-hydroxy-risperidone, not to be confused with the term "active agent" used elsewhere herein). For the latter plasma samples, the concentrations of 9-hydroxy-risperidone were calculated as the difference between the concentrations of the active moiety and those of risperidone. The quantification limits for the RIA methods were 0.20 ng/ml for risperidone and 0.50 ng/ml for the active moiety.

For each of the formulations, mean (±S.D., n=3) plasma concentrations of risperidone, 9-hydroxy-risperidone, and of the active moiety, were calculated. Ratios of the plasma concentrations of 9-hydroxy-risperidone to those of risperidone were calculated where possible. Peak plasma concentrations and peak times of risperidone, 9-hydroxy-risperidone, and their sum were determined by visual inspection of the data. AUC ("area under the curve") values of risperidone and 9-hydroxy-risperidone were calculated between zero time and time using the trapezoidal rule. The time *t* is the last time point at which concentrations of risperidone or 9-hydroxy-risperidone were higher than the limit of quantification in at least 1 out of 3 dogs. For dogs belonging to the same formulation group, AUCs were calculated up to the same end-time *t*, using the value of the quantification limit, if one concentration was lower than the quantification limit. If two consecutive concentrations were lower than the quantification limit, the concentration of the earlier sampling point was set equal to the quantification limit, and the concentration of the later sampling point was taken as zero. The AUCs were not extrapolated to infinity. The AUC of the active moiety was calculated as the sum of the AUCs of risperidone and 9-hydroxy-risperidone.

Mean or median plasma concentrations and/or pharmacokinetic parameters of risperidone, 9-hydroxy-risperidone, and the active moiety for formulations Prodex 2/3/4A/4B/4C, are given in Table 1. Mean plasma concentration-time curves for formulations Prodex 2/3/4A/4B/4C are in Figure 5. For each of the formulation groups, results are first discussed

for risperidone, then for 9-hydroxy-risperidone, and at last for the active moiety. For the active moiety, plasma concentrations are related to the anti-emetic effect in the apomorphine vomiting test.

After administration of formulations Prodex 2 up to Prodex 4C, mean peak plasma levels of risperidone were low. They were attained at largely different time points. The further release of risperidone from the different formulations proceeded gradually and was long-lasting. This resulted in low plasma concentrations of both risperidone and its metabolite. Mean peak times for 9-hydroxy-risperidone all ranged from 26 to 30 days. The plasma concentration-time profile of the active moiety was similar for formulations Prodex 2 up to Prodex 4C. At the beginning of the experiment, plasma concentrations of the active moiety showed a peak within 1 or 2 days, due to a rapid initial release of risperidone. The peak was followed by a decrease of the concentrations with a dip at 5-8 days. From day 8 on, concentrations increased again until day 20, after which time they remained at a more or less constant level during a period of, on average, 15 days. During this period, for each of the formulations, concentrations of the active moiety showed a second peak and concentrations were higher than for the first peak. The anti-emetic activity lasted 35 to 42 days for formulations Prodex 2, Prodex 4A, and Prodex 4B. For formulation Prodex 4C, it lasted 49 days, but without interruption in any of the dogs. The longest activity of formulation Prodex 4C paralleled the highest C_{max}, T_{max}, and AUC_{0-t} for the active moiety, in comparison with the other 4 formulations of the same group.

The duration of action of these microparticle-based risperidone formulations in the apomorphine-induced emesis test in dogs was also studied. Neuroleptics antagonized apomorphine-induced emesis by blocking dopamine D_2 receptors in the area postrema of the fourth ventricle. The test is generally used to predict the onset and duration of antipsychotic action of neuroleptics in man (Janssen *et al.*, *Arzneim.-Forsch./Drug Res.*

15: 1196-1206 (1965); Niemegeers *et al., Life Sci. 24*:2201-2216 (1979)). 9-OH-risperidone has a pharmacological profile that is virtually identical to that of its parent compound. Parent compound and active metabolite constitute together the "active moiety" that determines the biological activity of risperidone.

Apomorphine was administered subcutaneously at 0.31 mg/kg to the dogs twice a week, during the whole course of the experiment. The dogs were observed for vomiting during a 1-hour period after the administration of apomorphine. Complete absence of emesis for 1 hour after apomorphine challenge was considered to reflect significant anti-emetic activity. The duration of the anti-emetic action was defined as the time interval during which 2 out of 3 dogs were protected from emesis.

The formulations were injected in a volume of 0.5 ml into the biceps femoralis of one of the hind limbs at the level of the thigh. At several time intervals after the intramuscular injection, blood samples were taken and, immediately thereafter, the dogs were challenged with a dose of apomorphine. Complete absence of emesis within 1 h after apomorphine challenge (which is never observed in control animals; $n>1000$) was considered to reflect significant antiemetic activity.

Table 2 indicates whether the dogs were protected (+) or not protected (-) from apomorphine-induced emesis at the various time intervals after intramuscular injection of the depot formulations. All formulations showed an immediate onset of anti-emetic action.

TABLE 1 **Mean (±S.D.; n=3) or median plasma concentrations and mean (±S.D.; n=3) pharmacokinetic parameters of risperidone, 9-hydroxy-risperidone, and their sum (= the "active moiety") after intramuscular administration of risperidone depot formulations at 2.5 mg/kg to beagle dogs.**

	Prodex 2		Prodex 3		Prodex 4A	
Time (days)	RISP	9-OH RISP	RISP	9-OH RISP	RISP	9-OH RISP
0	≤0.20	≤0.50	≤0.20	≤0.50	≤0.20	≤0.50
0.042 (1 h)	8.36 ± 1.06	4.17 ± 1.71	21.4 ± 8.8	14.4 ± 9.1	3.25 ± 0.57	1.18 ± 0.50
0.208 (5 h)	2.87 ± 0.20	7.34 ± 2.02	7.55 ± 3.38	27.4 ± 22.0	2.61 ± 0.60	5.13 ± 1.08
1	1.25 ± 0.72	6.92 ± 3.88	2.90 ± 1.70	23.0 ± 17.8	1.13 ± 0.24	7.82 ± 3.55
4	0.67 ± 0.61	4.36 ± 3.32	1.22 ± 0.77	6.58 ± 3.07	0.74 ± 0.38	2.54 ± 1.20
7	0.35*	1.65 ± 1.24	1.96 ± 1.70	8.79 ± 6.72	0.39*	1.90 ± 1.52
11	0.41 ± 0.15	1.16 ± 0.35	1.52 ± 0.91	11.2 ± 11.7	2.40 ± 3.55	12.7 ± 20.2
14	-**	-**	4.36 ± 1.99	29.4 ± 25.0	2.23 ± 1.19	12.6 ± 15.0
18	-	-	6.33 ± 2.48	44.1 ± 35.4	4.28 ± 1.41	23.3 ± 12.5
21	-	-	8.61 ± 2.25	44.8 ± 26.3	6.97 ± 1.57	27.1 ± 11.3
25	6.79 ± 1.74	44.6 ± 13.6	9.08 ± 3.95	47.9 ± 19.5	6.03 ± 1.50	32.3 ± 2.8
29	6.84 ± 3.19	46.0 ± 15.1	9.26 ± 5.27	54.2 ± 33.6	6.52 ± 1.40	40.2 ± 3.6
32	4.97 ± 1.89	39.5 ± 36.6	5.60 ± 2.78	38.8 ± 25.2	3.81 ± 1.72	35.2 ± 16.3
35	3.61 ± 1.84	25.8 ± 11.5	4.70 ± 3.39	28.4 ± 21.9	2.55 ± 1.31	22.1 ± 14.4
39	1.44 ± 0.51	13.0 ± 7.1	2.01 ± 1.47	16.4 ± 9.6	1.13 ± 0.82	10.4 ± 6.4
42	1.05 ± 0.45	7.73 ± 3.77	1.31 ± 0.79	10.7 ± 6.5	0.68*	6.08 ± 4.26
46	≤0.20*	2.94 ± 1.35	0.45*	5.55 ± 4.04	≤0.20*	2.48 ± 1.81
49	-	-	0.23*	2.13 ± 1.34	≤0.20	1.23*

TABLE 1 Mean (±S.D.; n=3) or median plasma concentrations and mean (±S.D.; n=3) pharmacokinetic parameters of risperidone, 9-hydroxy-risperidone, and their sum (= the "active moiety") after intramuscular administration of risperidone depot formulations at 2.5 mg/kg to beagle dogs.

	Prodex 2		Prodex 3		Prodex 4A	
Time (days)	RISP	9-OH RISP	RISP	9-OH RISP	RISP	9-OH RISP
53	-	-	-	-	-	-
56	-	-	-	-	-	-
C_{max} (ng/ml)	8.61 ± 1.41	61.0 ± 19.7	21.4 ± 8.8	56.3 ± 32.2	7.75 ± 0.78	43.9 6.6
T_{max} (days)	10 ± 17	29 ± 4	0.042 ± 0.000	26 ± 2	25 ± 4	30 ± 2
AUC_{0-t} (ng.h/ml)	3212 ± 914	21496 ± 4854	5048 ± 2397	30632 ± 19866	3280 ± 576	19632 ± 8274
t (days)	46	46	49	49	46	49
	RISP + 9-OH RISP		RISP + 9-OH RISP		RISP + 9-OH RISP	
C_{max} (ng/ml)	67.3 ± 19.8		66.0 ± 37.0		49.6 ±6.7	
T_{max} (days)	29 ± 4		26 ± 2		30 ± 2	
AUC_{0-t} (ng.h/ml)	24708 ± 5341		35680 ± 22261		22912 ± 8822	

* Median value.
** No blood sampling from day 14 until day 25 of the experiment, due to absence of protection against apomorphine-induced vomiting. Concentrations in italics indicate antiemetic activity in at least 2 out of 3 dogs.

TABLE 1 Mean (±S.D.; n=3) or median plasma concentrations and mean (±S.D.; n=3) pharmacokinetic parameters of risperidone, 9-hydroxy-risperidone and their sum (= the "active moiety") after intramuscular administration of risperidone depot formulations at 2.5 mg/kg to beagle dogs.

	Prodex 4B		Prodex 4C	
Time (days)	RISP	9-OH RISP	RISP	9-OH RISP
0	≤0.20	≤0.50	≤0.20	≤0.50
0.042 (1 h)	3.32 ± 0.75	2.53 ± 0.79	15.5 ± 5.2	3.32 ± 2.18
0.208 (5 h)	1.52 ± 0.33	5.56 ± 2.43	15.1 ± 7.7	19.2 ± 6.2
1	1.22 ± 0.58	7.10 ± 3.40	4.49 ± 1.04	25.0 ± 7.1
4	0.58*	2.25 ± 1.00	2.00 ± 0.42	12.1 ± 2.5
7	0.35*	1.78*	1.47 ± 0.29	7.96 ± 0.74
11	0.53*	1.87*	3.23 ± 1.72	13.4 ± 4.6
14	4.06 ± 3.47	22.1 ± 20.3	7.67 ± 4.54	30.9 ± 17.8
18	1.41 ± 0.14	5.13 ± 0.85	8.15 ± 4.69	48.5 ± 34.5
21	7.22 ± 4.98	27.1 ± 21.1	13.1 ± 9.4	69.3 ± 41.4
25	5.39 ± 3.41	41.0 ± 29.7	8.37 ± 0.88	67.8 ± 28.0
29	4.66 ± 1.47	31.1 ± 13.3	13.8 ± 5.2	77.9 ± 17.7
32	3.50 ± 1.81	21.4 ±9.8	10.3 ± 4.5	80.9 ± 51.3
35	1.91 ± 0.71	14.9 ± 4.5	7.58 ± 3.49	61.4 ± 15.1
39	0.67 ± 0.16	7.15 ± 2.47	3.90 ± 1.34	31.2 ± 10.7
42	≤0.20*	3.83 ± 0.40	2.97 ± 1.35	23.2 ± 13.7
46	≤0.20*	1.08 ± 0.53	0.68 ± 0.39	10.4 ± 6.3
49	-	-	0.26*	6.04 ± 3.75
53	-	-	≤0.20*	2.98 ± 2.39
56	-	-	≤0.20*	1.89 ± 1.40

TABLE 1 Mean (±S.D.; n=3) or median plasma concentrations and mean (±S.D.; n=3) pharmacokinetic parameters of risperidone, 9-hydroxy-risperidone and their sum (= the "active moiety") after intramuscular administration of risperidone depot formulations at 2.5 mg/kg to beagle dogs.

	Prodex 4B		Prodex 4C	
Time (days)	RISP	9-OH RISP	RISP	9-OH RISP
C_{max} (ng/ml)	7.71 ± 4.23	42.6 ± 27.3	16.3 ± 6.6	95.4 ± 41.7
T_{max} (days)	24 ± 5	26 ± 2	0.097 ± 0.096	30 ± 2
AUC_{0-t} (ng.h/ml)	2648 ± 1199	15656 ± 8104	7424 ± 3018	46840 ± 19125
t (days)	46	46	56	56
	RISP + 9-OH RISP		RISP + 9-OH RISP	
C_{max} (ng/ml)	48.5 ± 29.8		108 ± 44	
T_{max} (days)	26 ± 2		30 ±2	
AUC_{0-t} (ng.h/ml)	18311 ± 9222		54264 ± 22055	

* Median value.
** No blood sampling from day 14 until day 25 of the experiment, due to absence of protection against apomorphine-induced vomiting. Concentrations in italics indicate antiemetic activity in at least 2 out of 3 dogs .

Table 2: **Protection (+) or no protection (-) from apomorphine-induced emesis in dogs at successive time intervals after intramuscular administration of microparticle-based depot formulations of the antipsychotic risperidone at an approximate dose level of 2.5 mg/kg**

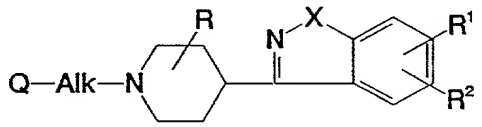
Form.	Prodex 2			Prodex 3			Prodex 4A			Prodex 4B			Prodex 4C		
Dog Weight (kg)	14.2	11.5	9.8	12.9	12.4	13.4	10.0	12.3	9.2	9.7	8.6	10.6	13.2	16.4	16.2
Volume (ml/dog)	0.5[3]	0.5[3]	0.5[3]	0.5[3]	0.5[3]	0.5[3]	0.5[3]	0.5[3]	0.5[3]	0.5[3]	0.5[3]	0.5[3]	0.5[3]	0.5[3]	0.5[3]
Dose (mg/kg)	2.5	2.5	2.8	2.5	2.5	2.5	2.5	2.3	2.6	2.5	2.5	2.6	2.4	2.4	2.5
Route	im	im	im	im	im	im	im	im	im	im	im	im	im	im	im
1 h	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+
5 h	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
1 d	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
4 d	-	-	+	+	-	+	+	+	-	-	-	+	+	+	+
7 d	-	-	-	-	+	+	-	-	-	-	-	+	+	+	+
11 d	-	-	-	+	+	+	+	+	-	-	-	+	+	+	+
14 d				+	+	+	+	+	+	-	+	+	+	+	+
18 d				+	+	+	+	+	+	+	+	+	+	+	+
21 d				+	+	+	+	+	+	+	+	+	+	+	+
25 d	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
29 d	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
32 d	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
35 d	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table 2:	Protection (+) or no protection (-) from apomorphine-induced emesis in dogs at successive time intervals after intramuscular administration of microparticle-based depot formulations of the antipsychotic risperidone at an approximate dose level of 2.5 mg/kg															
39 d	-	+	+	+	-	+	+	+	-	-	-	-	+	+	+
42 d	-	-	-	+	-	+	+	-	-	-	-	-	+	+	-
46 d	-	-	-	+	-	-	-	-	-	-	-	-	+	+	-
49 d	Stop			-	-	-	-	-	-	Stop			+	+	-
53 d				Stop			Stop						-	+	-
56 d													-	-	-
													Stop		

[3] Injection volume: 0.5 ml/dog; the concentration of the microparticles was adapted to the body weight.

What Is Claimed Is:

1. A method of treating warm blooded animals suffering from psychotic disorders comprising the administration thereto of a pharmaceutically effective amount of a biodegradable and biocompatible microparticle composition comprising a 1,2-benzazole of the formula



and the pharmaceutically acceptable acid addition salts thereof, wherein

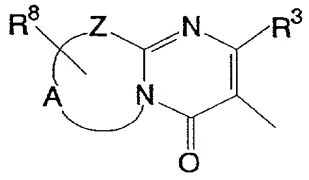
R is hydrogen or alkyl of 1 to 6 carbon atoms;

R^1 and R^2 are independently selected from the group consisting of hydrogen, halo, hydroxy, alkyloxy of 1 to 6 carbon atoms, and C alkyl of 1 to 6 carbon atoms;

X is O or S;

Alk is C_{1-4} alkanediyl; and

Q is a radical of formula



wherein

R^3 is hydrogen or alkyl of 1 to 6 carbon atoms;

Z is —S—, $—CH_2—$, or $—CR^4=CR^5—$; where R^4 and R^5 are independently selected from the group consisting of hydrogen or alkyl of 1 to 6 carbon atoms;

A is a bivalent radical $—CH_2—CH_2—$, $—CH_2—CH_2—CH_2—$ or $CR^6=CR^7—$; where R^6 and R^7 are independently selected from the group consisting of hydrogen, halo, amino or alkyl of 1 to 6 carbon atoms; and

R^8 is hydrogen or hydroxyl;

within a polymeric matrix.

2. The method of claim 1, wherein the polymeric matrix material of said microparticle is selected from the group consisting of poly(glycolic acid), poly-D,L-lactic acid, poly-L-lactic acid, copolymers of the foregoing, poly(aliphatic carboxylic acids), copolyoxalates, polycaprolactone, polydioxonone, poly(ortho carbonates), poly(acetals), poly(lactic acid-caprolactone), polyorthoesters, poly(glycolic acid-caprolactone), polyanhydrides, albumin, casein, and waxes.

3. The method of claim 1, wherein said 1,2-benzazole comprises 1 to 90 wt.% of said microparticles.

4. The method of claim 1, wherein said 1,2-benzazole comprises about 35 to 40 wt.% of said microparticles.

5. The method of claim 1, wherein said microparticles range in size from 1 to 500 microns.

6. The method of claim 1, wherein said microparticles range in size from 25 to 180 microns.

7. The method of claim 1, wherein said microparticles are formulated in a liquid injection vehicle.

8. The method of claim 7, wherein said liquid vehicle is selected from the group consisting of

A. physiological saline solution and

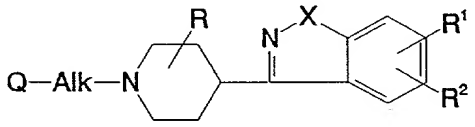
B. an aqueous solution of carboxymethyl cellulose with a surfactant.

9. The method of claim 1, wherein said microparticles are administered by intra-muscular injection.

10. The method of claim 1, wherein said microparticles are administered by subcutaneous injection.

11. The method of claim 1, wherein the 1,2-benzazole is selected from the group consisting of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl)ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one and the pharmaceutically acceptable acid addition salts thereof.

12. A pharmaceutical composition comprising a biodegradable and biocompatible microparticle composition comprising a 1,2-benzazole of the formula



and the pharmaceutically acceptable acid addition salts thereof, wherein

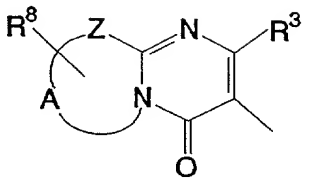
R is hydrogen or alkyl of 1 to 6 carbon atoms;

R^1 and R^2 are independently selected from the group consisting of hydrogen, halo, hydroxy, alkyloxy of 1 to 6 carbon atoms, and C alkyl of 1 to 6 carbon atoms;

X is O or S;

Alk is C_{1-4} alkanediyl; and

Q is a radical of formula



wherein

R^3 is hydrogen or alkyl of 1 to 6 carbon atoms;

Z is —S—, —CH_2—, or —CR^4=CR^5—; where R^4 and R^5 are independently selected from the group consisting of hydrogen or alkyl of 1 to 6 carbon atoms;

A is a bivalent radical —CH_2—CH_2—, —CH_2—CH_2—CH_2— or CR^6=CR^7—; where R^6 and R^7 are independently selected from the group consisting of hydrogen, halo, amino or alkyl of 1 to 6 carbon atoms; and

R^8 is hydrogen or hydroxyl;

within a polymeric matrix.

13. The pharmaceutical composition of claim 12, wherein the polymeric matrix material of said microparticle is selected from the group consisting of poly(glycolic acid), poly-D,L-lactic acid, poly-L-lactic acid, copolymers of the foregoing, poly(aliphatic carboxylic acids), copolyoxalates, polycaprolactone, polydioxonone, poly(ortho carbonates), poly(acetals), poly(lactic acid-caprolactone), polyorthoesters, poly(glycolic acid-caprolactone), polyanhydrides, albumin, casein, and waxes.

14. The pharmaceutical composition of claim 12, wherein said 1,2-benzazole comprises 1 to 90 wt.% of said microparticles.

15. The pharmaceutical composition of claim 12, wherein said 1,2-benzazole comprises about 35 to 40 wt.% of said microparticles.

16. The pharmaceutical composition of claim 12, wherein said microparticles range in size from 1 to 500 microns.

17. The pharmaceutical composition of claim 12, wherein said microparticles range in size from 25 to 180 microns.

18. The pharmaceutical composition of claim 12, wherein said microparticles are formulated in a liquid injection vehicle.

19. The pharmaceutical composition of claim 18, wherein said liquid vehicle is selected from the group consisting of

A. physiological saline solution and

B. an aqueous solution of carboxymethyl cellulose with a surfactant.

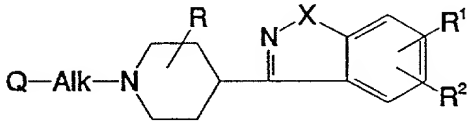
20. The pharmaceutical composition of claim 12, wherein said microparticles are administered by intra-muscular injection.

21. The pharmaceutical composition of claim 12, wherein said microparticles are administered by subcutaneous injection.

22. The pharmaceutical composition of claim 12, wherein the 1,2-benzazole is selected from the group consisting of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl)ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one and the pharmaceutically acceptable acid addition salts thereof.

23. A method of inhibiting serotonergic overactivity or dopaminergic overstimulation in animals wherein said method comprises administration

of a biodegradable and biocompatible microparticle composition comprising a 1,2-benzazole of the formula



and the pharmaceutically acceptable acid addition salts thereof, wherein

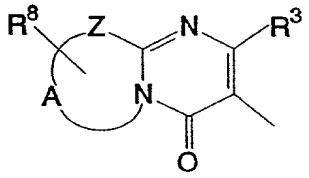
R is hydrogen or alkyl of 1 to 6 carbon atoms;

R^1 and R^2 are independently selected from the group consisting of hydrogen, halo, hydroxy, alkyloxy of 1 to 6 carbon atoms, and C alkyl of 1 to 6 carbon atoms;

X is O or S;

Alk is C_{1-4} alkanediyl; and

Q is a radical of formula



wherein

R^3 is hydrogen or alkyl of 1 to 6 carbon atoms;

Z is —S—, —CH_2—, or —CR^4=CR^5—; where R^4 and R^5 are independently selected from the group consisting of hydrogen or alkyl of 1 to 6 carbon atoms;

A is a bivalent radical —CH_2—CH_2—, —CH_2—CH_2—CH_2— or CR^6=CR^7—; where R^6 and R^7 are independently selected from the group consisting of hydrogen, halo, amino or alkyl of 1 to 6 carbon atoms; and

R^8 is hydrogen or hydroxyl;

within a polymeric matrix.

24. The method of claim 23, wherein the polymeric matrix material of said microparticle is selected from the group consisting of poly(glycolic acid), poly-D,L-lactic acid, poly-L-lactic acid, copolymers of the foregoing, poly(aliphatic carboxylic acids), copolyoxalates, polycaprolactone, polydioxonone, poly(ortho carbonates), poly(acetals), poly(lactic acid-caprolactone), polyorthoesters, poly(glycolic acid-caprolactone), polyanhydrides, albumin, casein, and waxes.

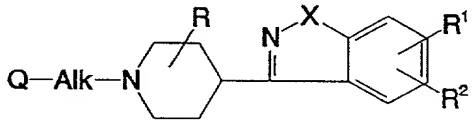
25. The method of claim 23, wherein said 1,2-benzazole comprises about 35 to 40 wt.% of said microparticles.

26. The method of claim 23, wherein said microparticles range in size from 25 to 180 microns.

27. The method of claim 23, wherein the 1,2-benzazole is selected from the group consisting of 3–[2–[4–(6–fluoro-1,2-benzisoxazol-3–yl)-1-piperidinyl)ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one and the pharmaceutically acceptable acid addition salts thereof.

Abstract of the Disclosure

The invention relates to a pharmaceutical composition comprising a biodegradable and biocompatible microparticle composition comprising a 1,2-benzazole of the formula



and the pharmaceutically acceptable acid addition salts thereof, wherein

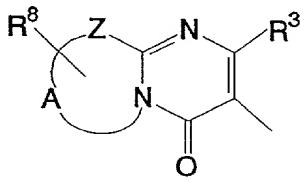
R is hydrogen or alkyl of 1 to 6 carbon atoms;

R^1 and R^2 are independently selected from the group consisting of hydrogen, halo, hydroxy, alkyloxy of 1 to 6 carbon atoms, and C alkyl of 1 to 6 carbon atoms;

X is O or S;

Alk is C_{1-4} alkanediyl; and

Q is a radical of formula



wherein

R^3 is hydrogen or alkyl of 1 to 6 carbon atoms;

Z is —S—, —CH_2—, or —CR^4=CR^5—; where R^4 and R^5 are independently selected from the group consisting of hydrogen or alkyl of 1 to 6 carbon atoms;

A is a bivalent radical —CH_2—CH_2—, —CH_2—CH_2—CH_2— or CR^6=CR^7—; where R^6 and R^7 are independently selected from the group consisting of hydrogen, halo, amino or alkyl of 1 to 6 carbon atoms; and

R^8 is hydrogen or hydroxyl

within a polymeric matrix.

5

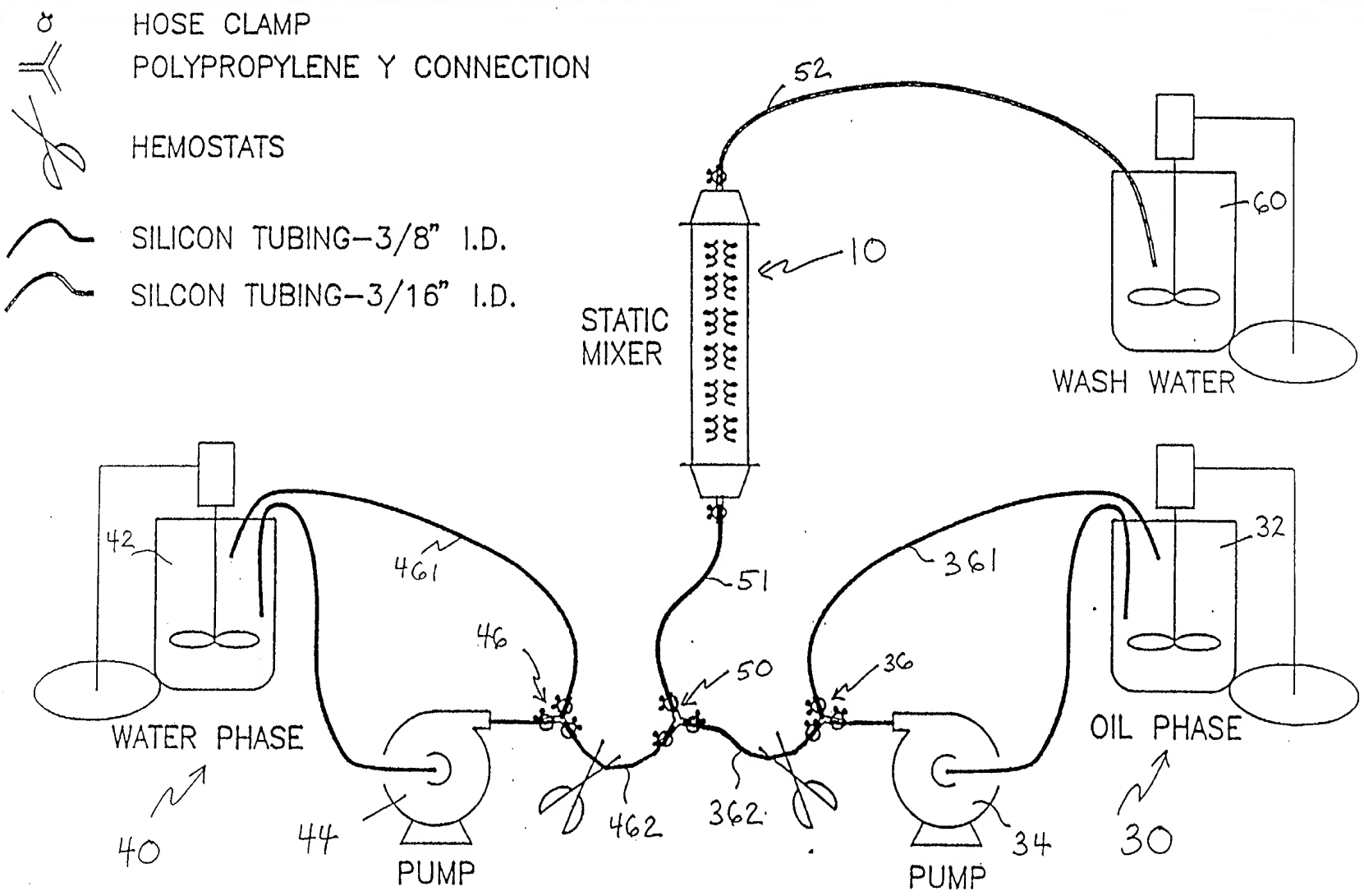
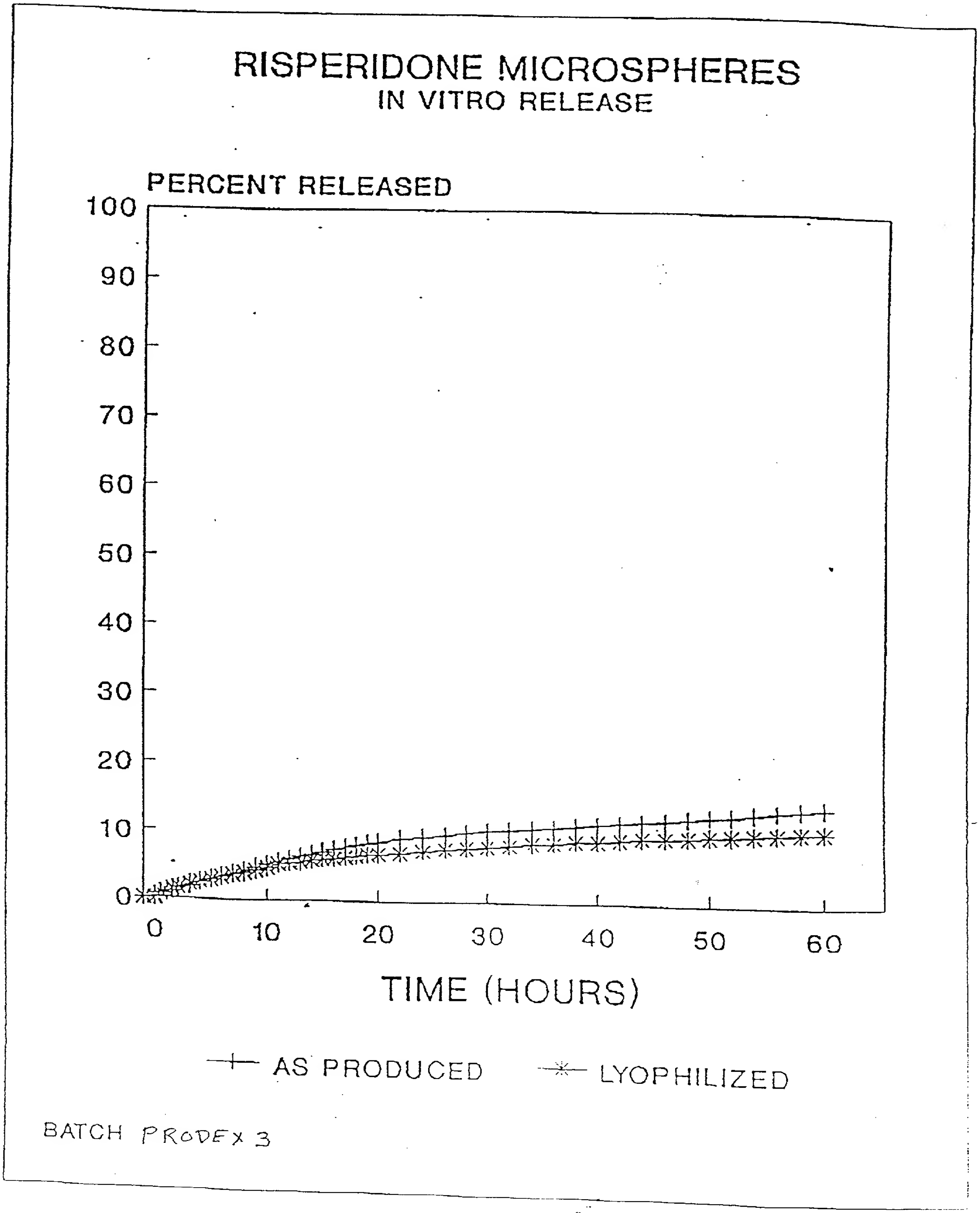

HOSE CLAMP
POLYPROPYLENE Y CONNECTION
HEMOSTATS
SILICON TUBING–3/8" I.D.
SILCON TUBING–3/16" I.D.
52
60
10
STATIC MIXER
WASH WATER
42
461
46
51
361
32
50
36
WATER PHASE
OIL PHASE
40
44
PUMP
462
362
PUMP
34
30

Figure 1


RISPERIDONE MICROSPHERES
IN VITRO RELEASE
PERCENT RELEASED
100
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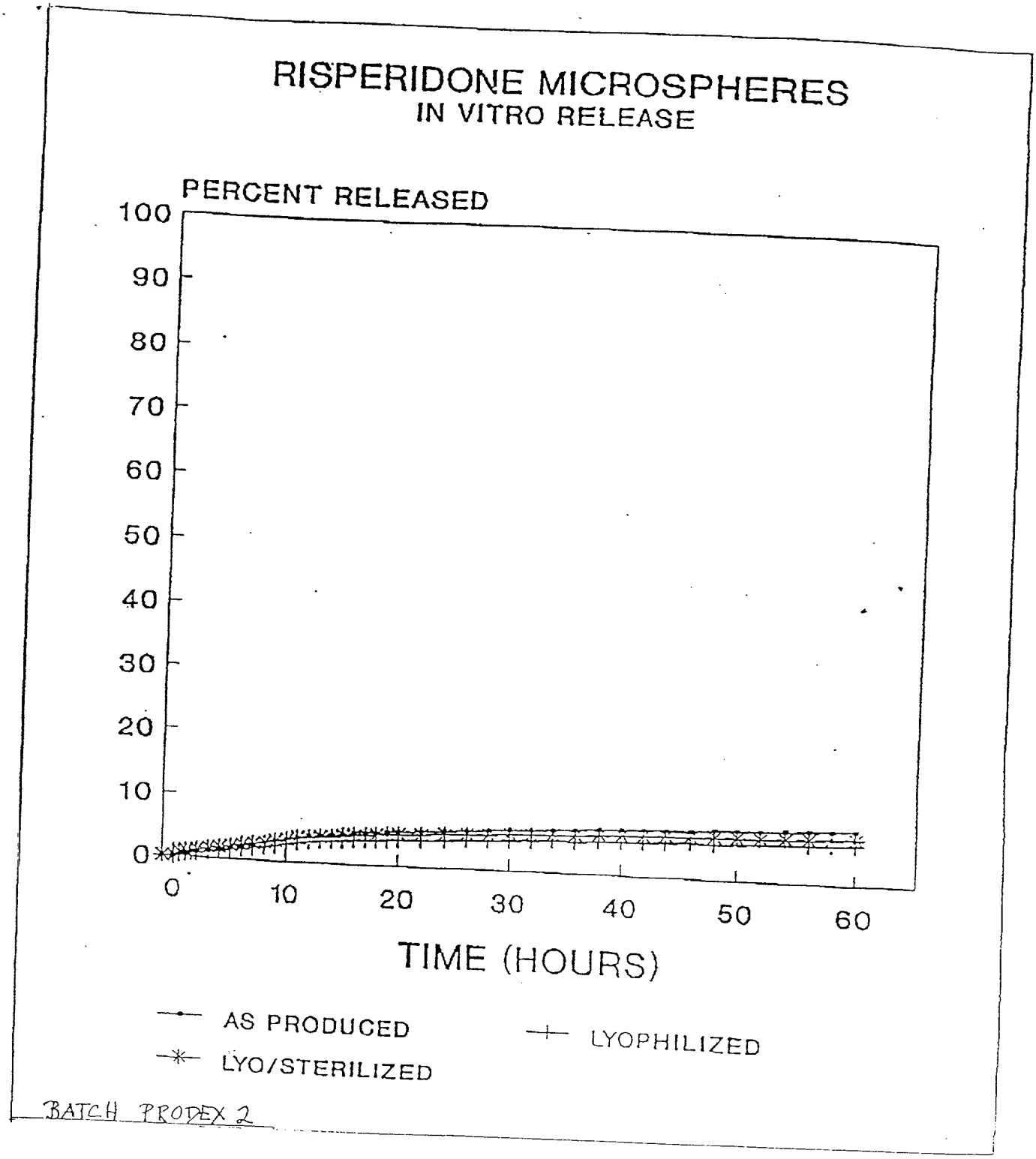
60
TIME (HOURS)
AS PRODUCED
LYOPHILIZED
BATCH PRODEX 3

Figure 2


RISPERIDONE MICROSPHERES
IN VITRO RELEASE
PERCENT RELEASED
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40
50
60
TIME (HOURS)
AS PRODUCED
LYOPHILIZED
LYO/STERILIZED
BATCH PRODEX 2

Figure 3

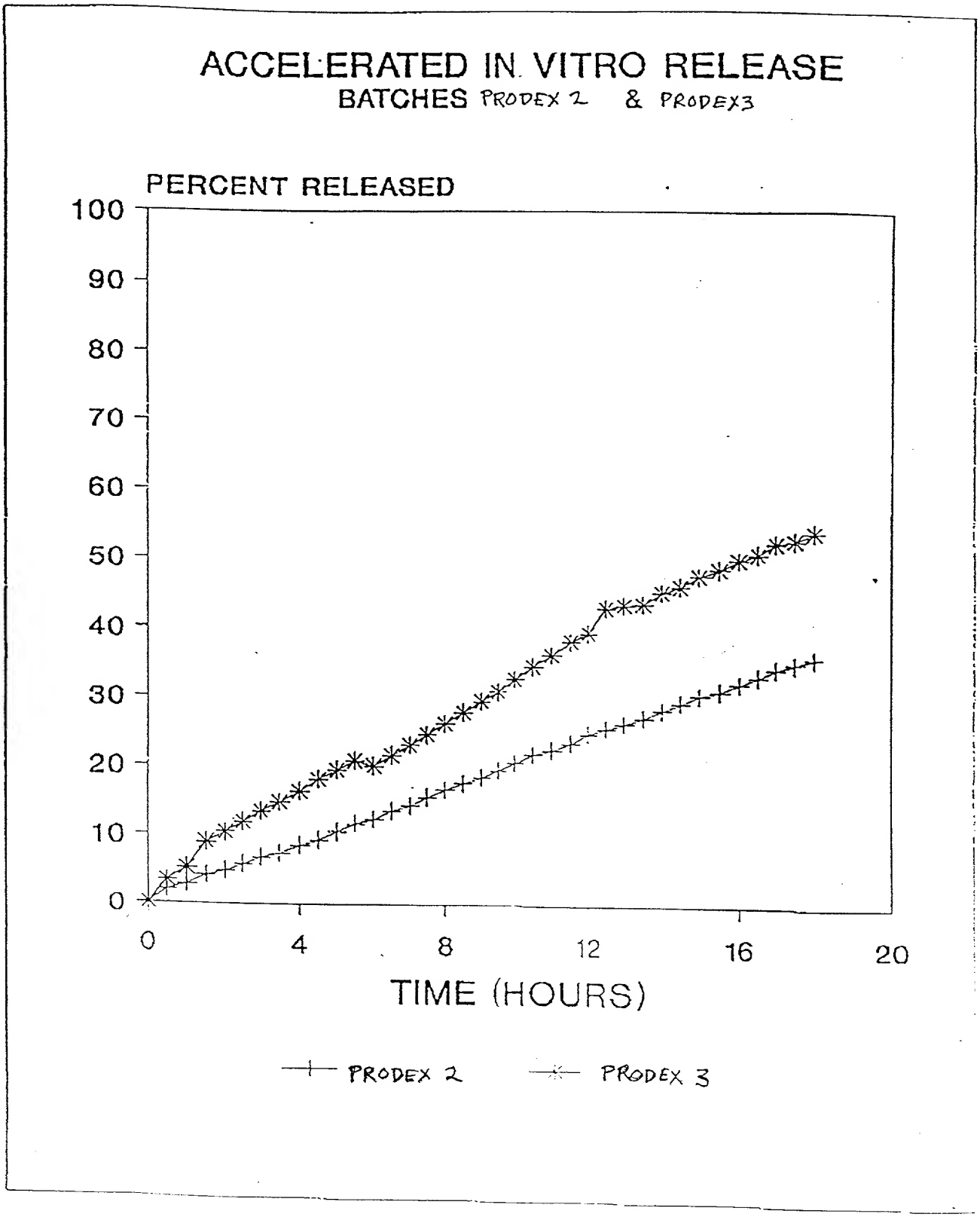
ACCELERATED IN VITRO RELEASE
BATCHES PRODEX 2 & PRODEX3
PERCENT RELEASED
100
90
80
70
60
50
40
30
20
10
0
0
4
8
12
16
20
TIME (HOURS)
PRODEX 2
PRODEX 3

Figure 4

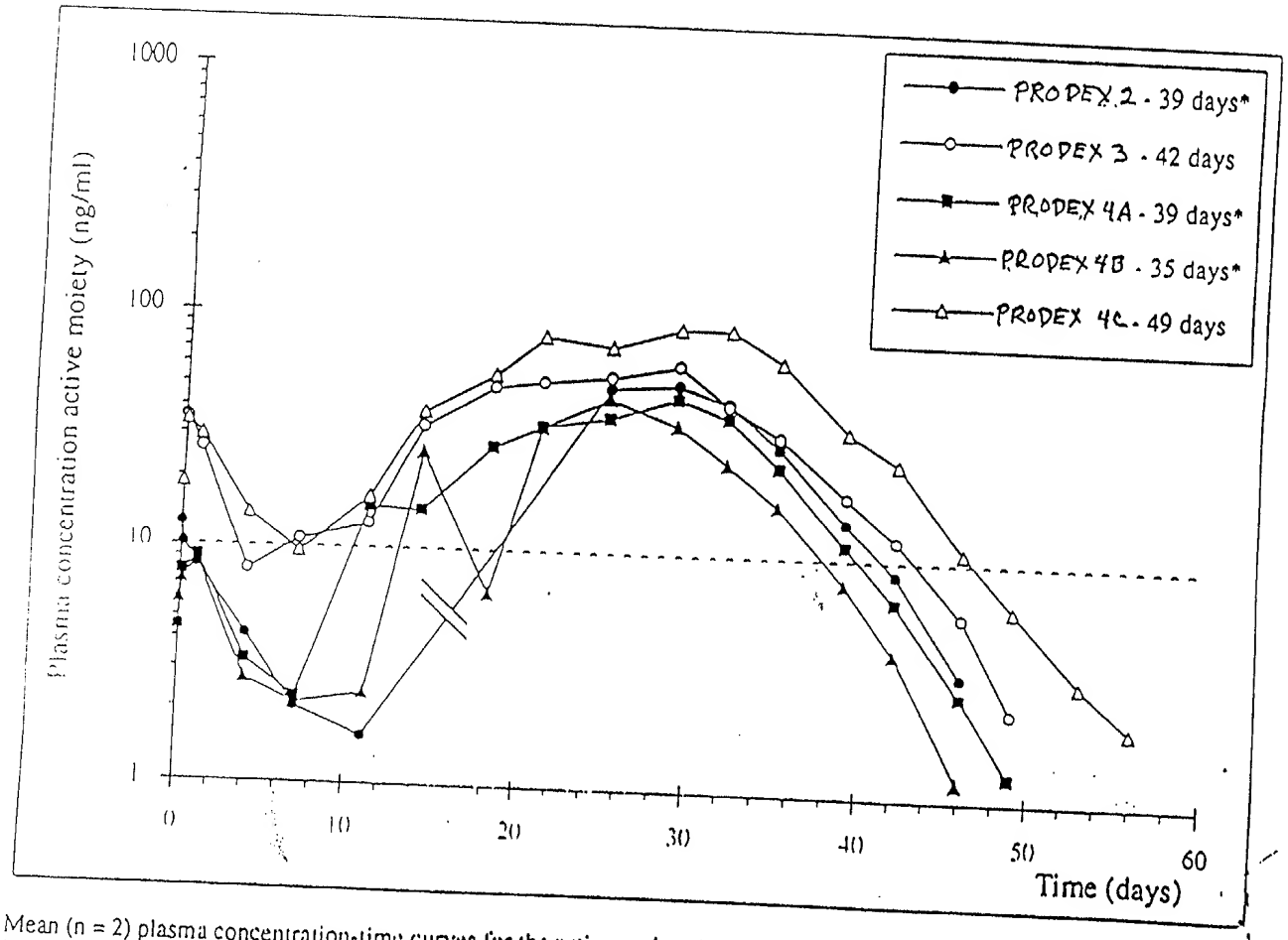

Figure 5 Mean (n = 2) plasma concentration-time curves for the active moiety (sum of risperidone and 9-hydroxy-risperidone) after single intramuscular administration of risperidone depot formulations at an approximate dose of 2.5 mg/kg to beagle dogs.
The period of anti-emetic activity (in at least 2 out of 3 dogs) in the apomorphine vomiting test is given in the legend for each of the formulations. An asterisk (*) indicates that the anti-emetic activity is interrupted in at least 2 out of 3 dogs at the beginning of the study.
The broken line indicates an approximate lowest minimum plasma concentration necessary for anti-emetic activity. The //sign indicates that for formulation PRODEX 2 no blood was sampled on days 14, 18 and 21.

COPY

Declaration and Power of Attorney for Patent Application
English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

MICROENCAPSULATED 3-PIPERIDINYL-SUBSTITUTED 1,2-BENZISOXAZOLES AND 1,2-BENZISOTHIAZOLES

the specification of which

(check one)

☐ is attached hereto.

☒ was filed on November 19, 1993
Serial No. 08/154,403
amended on _____.
(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed	
(Number)	(Country)	(Day Month Year Filed)	☐ Yes	☐ No
(Number)	(Country)	(Day Month Year Filed)	☐ Yes	☐ No

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application.

(Application Serial No.)	(Filing Date)	(Status)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. (*list name and registration number*)

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(Supply similar information and signature for subsequent joint inventors, if any).

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